

## A Case of Glomeruloid Hemangioma in a Patient with Multicentric Castleman's Disease

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Glomeruloid hemangioma is a histologically distinctive cutaneous angioma which is rarely described in patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome and multicentric Castleman's disease. We report an additional case of glomeruloid hemangioma in a 30-year-old Korean woman with multicentric Castleman's disease showing features of POEMS syndrome. Histopathology revealed multiple dermal dilated vascular spaces composed of a conglomerate of capillaries, resulting in structures reminiscent of renal glomeruli. Periodic acid-Schiff-positive and diastase-resistant eosinophilic globules were found within the cytoplasm of vacuolated endothelial cells. The endothelial cells lining the capillary loops showed positive immunostaining for factor VIII-related antigen and CD31. (*Ann Dermatol* 14(4) 220~225, 2002).

**Key Words :** Glomeruloid hemangioma, Castleman's disease

Glomeruloid hemangioma (GH) is a cutaneous angioma of unique histopathological morphology that was first named by J.K.C. Chan and colleagues<sup>1</sup> in 1990. This rare hemangioma derives its name from its distinctive histological resemblance to renal glomeruli and occurs in the setting of multicentric Castleman's disease and POEMS syndrome, a multisystemic disorder consisting of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes<sup>2</sup>. Many patients with POEMS syndrome show overlapping features with multicentric Castleman's

disease and the characteristic angiofollicular lymphoid hyperplasia of lymph nodes<sup>3</sup>. To the best of our knowledge, the pathogenetic mechanism of GH remains incomplete. In this report we describe the clinical data and histopathological features of GH in a 30-year-old Korean woman with multicentric Castleman's disease showing features of POEMS syndrome.

### CASE REPORT

In July 2000, a 30-year-old Korean woman was referred to our clinic with multiple skin lesions on trunk. Two years before her visit, progressive abdominal distention developed and the CT scan revealed focal nodular pulmonary lesions, diffuse hepatosplenomegaly, bilateral perinephric infiltration, enlargement of both kidneys, and multiple hilar, mediastinal, and retroperitoneal lymphadenopathies (Fig. 1). In May 1999, palpable axillary and inguinal masses were present and the subsequent lymph node biopsies showed exuberant proliferation of hyalinized capillaries perforating follicular centers, confirming the diagnosis of Castleman's disease of hyaline vascular type (Fig. 2). Further endocrinological eval-

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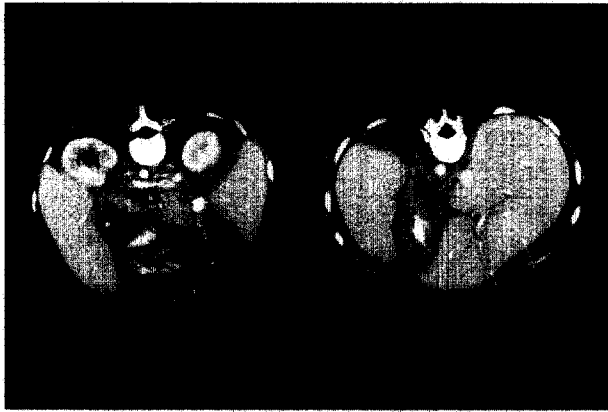


Fig. 1. Hepatosplenomegaly and globular enlargement of kidneys (CT scan, abdominal window setting)

uation revealed hypothyroidism, hyperprolactinemia, and adrenal insufficiency. However, no diagnostic abnormalities were seen in serum and urine protein electrophoresis. No peripheral or central sensory-motor neuropathies were observed either. She was treated with prednisolone, cyclophosphamide, spironolactone, and thyroxine replacement. Skin lesions appeared one month prior to her visit to our clinic.

Skin examination revealed multiple erythematous dome-shaped papules with average diameter of 3mm over her breast, abdominal wall, and both axillary skin (Fig. 3A, 3B). Punch biopsy was undertaken from the erythematous papule on trunk.

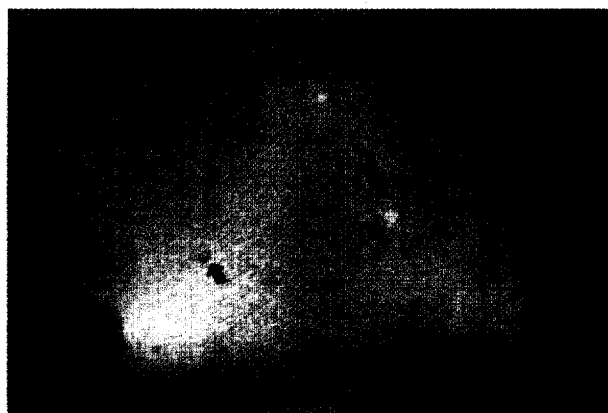
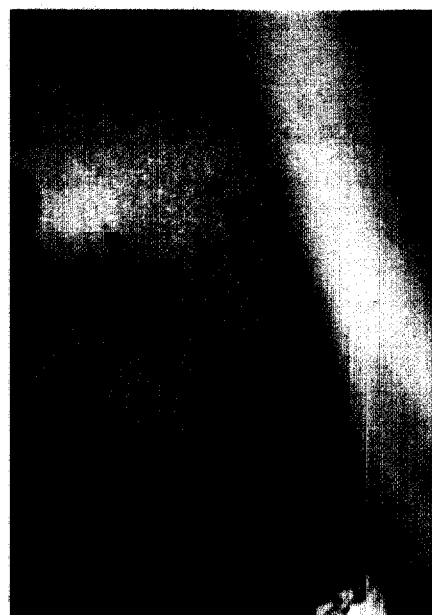


Fig. 3. A, B. Multiple slightly erythematous papules and nodules on chest, axillae, and upper extremities



Fig. 2. Histopathology of the involved lymph node revealed many lymphoid follicles penetrated by hyalinized capillaries, which are characteristic features of Castleman's disease of hyaline vascular type (Inguinal lymph node. H & E,  $\times 40$ ).

The lesion was covered by normal epidermis and ectatic vascular channels were present throughout the dermis (Fig. 4). The vascular spaces showed an intravascular proliferation of endothelium and occasional conglomeration of capillaries resulting in focal architecture of glomeruloid tufts. Additional deeper section of the paraffin-embedded specimen showed a more typical glomeruloid proliferation of blood-filled capillary loops reminiscent of renal glomeruli (Fig. 5). The majority of the endothelial cells lining the capillary loops were flat and con-



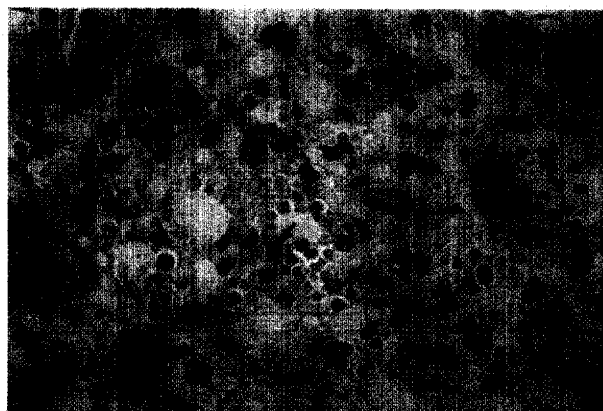


**Fig. 4.** Throughout the dermis there were ectatic vascular spaces filled with capillary loops (Skin. H & E,  $\times 12.5$ ).



**Fig. 5.** Conglomeration of capillary loops resulted in the structures resembling renal glomeruli (Skin. H & E,  $\times 100$ ).

endothelial cells stained positive for factor VIII-related antigen and CD31. No fibrous cores or thrombi were found and the endothelial cells lack significant cytologic atypia. These histopathological findings were consistent with those of GH, first described by



**Fig. 6.** A. Capillary loops were lined by plump endothelial cells containing intracytoplasmic vacuoles. B. Also note the abundant homogenous eosinophilic globules (arrows) (Skin H & E,  $\times 400$ ).

tained scanty cytoplasm. The rest of the endothelial cells were composed of plump cells rich in pale cytoplasm possessing various amount of intracytoplasmic vacuoles (Fig. 6A). The plump cells possessed a striking degree of homogenous eosinophilic globules, or droplets, which were variable in size and stained a lighter color compared with red blood cells (Fig. 6B). They stained positive for periodic acid-Schiff (PAS) after diastase digestion. Further immunohistochemical studies revealed that the en-

Chan et al.<sup>1</sup> and later reported by other authors<sup>4,7</sup>. The tissue block of the punch biopsy specimen was no longer retrievable for further studies.

## DISCUSSION

Castleman's disease is a clinicopathologic entity of unknown etiology which is characterized by angiofollicular lymphoid hyperplasia in lymph nodes

with multiorgan involvement. POEMS syndrome is a multisystemic disease characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathies, and skin changes. Many patients with multicentric Castleman's disease show clinical features of POEMS syndrome whereas most patients with POEMS syndrome show histopathological findings of Castleman's disease in lymph node biopsies. Thus, these two conditions are regarded as overlapping entities<sup>3</sup>.

The associated skin changes seen in POEMS syndrome include hyperpigmentation, hypertrichosis, thickening of skin, increased sweating, anasarca, clubbing of fingers, white nails, and angiomas<sup>6</sup>. The occurrence of multiple cutaneous angiomas in POEMS syndrome is a rare, but well-documented phenomenon occurring in 24-44% of Japanese patients<sup>4</sup>. The angiomas usually show the histopathologic feature of cherry-type capillary hemangiomas, with branching, haphazardly arranged vascular lumens lined by flat endothelium in mid- to lower dermis<sup>9</sup>.

In 1990, Chan *et al*<sup>1</sup> described a histopathologically distinctive cutaneous hemangioma occurring in two patients with multicentric Castleman's disease associated with POEMS syndrome. The lesions were multiple, and appeared as red to purple papules over the trunk and proximal limbs. Microscopically, ectatic dermal vascular spaces were filled with aggregates of capillaries, resembling the structures of renal glomeruli. The capillary loops were lined by occasional plump "stromal" cells possessing clear vacuoles and PAS-positive eosinophilic globules. These cells showed an immunohistochemical profile of endothelial cells. Because of the striking histological resemblance to

renal glomeruli, they named this distinctive angioma as GH. Since then, other authors<sup>4-7</sup> reported further patients in whom cutaneous angiomas of the glomeruloid type was in association with POEMS syndrome or multicentric Castleman's disease. Most of the reported cases showed clinical, histopathological, and immunohistochemical features consistent with those described by Chan *et al*<sup>1</sup>. Although many cases of multicentric Castleman's disease and POEMS syndrome were reported in Korean literature, we could not find any cases describing the presence of cutaneous GH among them.

Although various other vascular proliferative conditions including acquired tufted angioma, intravascular pyogenic granuloma, papillary endothelial hyperplasia (Masson's hemangioma), reactive angioendotheliomatosis, and endovascular papillary angioendothelioma (Dabska tumor) should be differentiated<sup>1,4-6,8,10</sup>, GH is generally not difficult to diagnose histopathologically if a lesion shows typical glomeruloid proliferation of capillaries and abundant eosinophilic globules. Because the first section of our biopsy specimen didn't contain the very deep dermis, we found only the focal glomeruloid tufts within the vascular proliferation rather than fully developed glomeruloid architecture described by Chan *et al*<sup>1</sup>. However, subsequent deeper section showed vascular spaces almost fully occupied by glomeruloid proliferation of capillaries combined with striking degree of eosinophilic globules, which helped us to make a histopathological diagnosis of GH.

Previous reports described GH associated with other angiomatous lesions (Table 1). Chan *et al*<sup>1</sup> and Kishimoto *et al*<sup>7</sup> noted that they found a feature of

**Table 1.** Summary of the previously reported cases of GH

Age/Sex	Underlying Disease	Histopathology	Reference
54/F	POEMS, mCD	GH, cherry angioma-like	Chan <i>et al</i> <sup>1</sup> .
40/F	POEMS, mCD	GH, cherry angioma-like	Chan <i>et al</i> <sup>1</sup> .
49/F	POEMS	GH	Tsai <i>et al</i> <sup>4</sup> .
58/M	POEMS	GH, tufted angioma-like	Rongioletti <i>et al</i> <sup>5</sup> .
44/M	POEMS, mCD	GH, immature angioma	Yang <i>et al</i> <sup>6</sup> .
57/F	POEMS	GH	Kishimoto <i>et al</i> <sup>7</sup> .
30/F	POEMS, mCD	GH, cherry angioma-like	present case

F, female; M, male; mCD, multicentric Castleman's disease; GH, glomeruloid hemangioma

glomeruloid/cherry type capillary hemangioma in their cases. The case reported by Rongioletti *et al.*<sup>5</sup> showed admixed features of glomeruloid/tufted angioma. Yang *et al.*<sup>6</sup> described a patient in whom the initial biopsy revealed an immature vascular tumor that could not be classified precisely and the second one, taken two months later, indicated GH. Our patient also showed coexistence of both cherry-type capillary hemangioma and typical GH in the same biopsy specimen. As first proposed by Chan *et al.*<sup>1</sup>, various types of hemangiomas found in POEMS syndrome may reflect merely different stages of development of the same lesion or different degrees of endothelial proliferation.

Some authors<sup>6,11</sup> suggested that GH is thought to be a reactive endothelial proliferation in response to angiogenic stimuli, rather than a true neoplasm. Later, Kishimoto *et al.*<sup>7</sup> proposed that it may occur through two different mechanisms (angiogenesis and vasculogenesis), based on the immunophenotypic profile of endothelial cells. Indeed, previous study<sup>12</sup> revealed an overproduction of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF), a potent candidate for angiogenesis and vasculogenesis, in POEMS syndrome. Nevertheless, the precise mechanism of glomeruloid proliferation of endothelial cells remains unclear. In addition, it should be mentioned that the presence of eosinophilic globules is not a unique diagnostic finding for GH because similar structures have also been demonstrated in other vasculoproliferative lesions such as targetoid hemosiderotic hemangioma, angiosarcoma, and Kaposi's sarcoma<sup>13,14</sup>. The eosinophilic globules are thought to represent immunoglobulin<sup>1,5,15</sup>, or erythrophagosomes<sup>13,17</sup>. Taken together with previous studies, GH may reflect a reactive endothelial proliferative condition provoked by certain angiogenic or vasculogenic stimuli, resulting in the appearance of typical glomeruloid structures with accumulation of proteins (may be immunoglobulins) absorbed during the circulation.

Although some cases of GH (including ours) did occur in patients with multicentric Castleman's disease, Tsai *et al.*<sup>4</sup> proposed that GH is a distinctive vascular proliferation which may be a specific cutaneous marker of POEMS syndrome, based on the fact that all the reported cases of GH occurring in patients with Castleman's disease were associated with clinical features of POEMS syndrome. It is

interesting that two cases<sup>16,17</sup> of cutaneous angiomas occurring in patients with POEMS syndrome reported before Chan *et al.*<sup>1</sup> described the typical histopathological features of GH. Furthermore, glomeruloid differentiation of cutaneous angiomas was also described in a patient with multiple myeloma<sup>10</sup>, a well-known clinical spectrum of POEMS syndrome<sup>16</sup>. Our patient didn't fulfill the diagnostic criteria of POEMS syndrome because she presented neither polyneuropathies nor monoclonal gammopathies, but the profound endocrinologic abnormalities and multiple organomegalies imply the future development of full-blown POEMS syndrome (the pathogenetic link between Castleman's disease and POEMS syndrome is fully discussed in a New England Journal of Medicine Weekly Clinicopathological Exercise, 1987<sup>3</sup>). In this context, we agree that GH should be regarded as a unique cutaneous marker of POEMS syndrome.

In conclusion, we suggest that the physician caring for a patient with a histopathological diagnosis of GH or other cutaneous angiomas showing focal glomeruloid differentiation should be alert to the potential development of full-blown POEMS syndrome. A thorough evaluation and follow-up is recommended in these patients.

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